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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/832,648	04/11/2001	Cy A. Stein	0575/55669-Z/JPW/BJA	2605

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EXAMINER	
EPPS FORD, JANET L	

ART UNIT	PAPER NUMBER
1635	17

DATE MAILED: 03/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/832,648	STEIN, CY A.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 February 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9,26-30 and 36-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,26-30 and 36-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2-08-02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments

2. Applicant's arguments with respect to claims 9, 26-30 and 36 over 35 USC § 103(a) have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 103

3. Claims 37-45, 55, 58, and 63-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pollman et al. and Gibbons et al. (US Patent No. 5,776,905) in view of Agrawal, and Summerton.

4. Claim 63 and 64 are drawn to a composition comprising an antisense oligonucleotide comprising consecutive nucleotides, the nucleotide sequence of which is set forth in SEQ ID NO: 2. Claim 65 is drawn to a method of promoting the regression of vascular lesions comprising introducing antisense oligonucleotides shown to be effective in reducing bcl-x_L expression into a vascular cell.

Pollman teach inhibition of neo-intimal cell bcl-x expression comprising transfecting a composition comprising Lipofectamine and an antisense oligonucleotide directed against bcl-x into atheromatous (i.e. vascular) lesions in the rabbit carotid artery (Methods section, p. 226). Specific down regulation of the bcl-x_L splice isoform resulted in regression of atheromatous lesions (see Figure 8, page 226). Additionally, Pollman et al. discloses 3 phosphorothioate modified antisense oligonucleotides, wherein antisense sequence-3 (#3; see Methods section, page 226) comprises the consecutive nucleotide sequence of SEQ ID NO: 2 of the instant application. Additionally, Gibbons et al. teach

a method for reducing the dimensions of a neointimal vascular lesion in a patient comprising localized delivery of an antisense oligonucleotide that inhibits the expression of bcl-x_L (col.2 lines 28-42).

Gibbons et al. teach administration of antisense oligonucleotides comprising methods known in the art for enhancing the uptake if nucleic acids by cells, for example delivery systems include Sendai virus-liposomes, cationic liposomes polymeric gels or matrices, and porous balloon catheters (col. 7, lines 45-60). Additionally, Gibbons et al. teach that the antisense oligonucleotides used in the method for reducing the expression of bcl-x_L in cells may comprise modifications to enhance oligonucleotide intracellular stability and binding affinity. In a specific embodiment Gibbons et al. teach that the 2'-OH ribose sugar may be altered to form 2'-O-methyl (col. 5, lines 6-28). [It is noted that since the specification as filed does not clearly define what the term "-OMe" is intended to encompass, this term is interpreted as encompassing either "2'-O-methyl" or "2'-O-methoxy."]

However, Pollman et al. and Gibbons et al. do not teach antisense compounds comprising 5-methyl cytidine modifications or morpholino subunit structures.

Agrawal teaches 5-methyl cytidine modification of nucleobases, this reference also teaches that substituted pyrimidines such as 5-methyl cytidine substitutions confers increased stability of nucleic acid duplexes. In addition, Agrawal teaches that 5-methyl cytidine modifications produce fewer side effects than conventional phosphorothioate oligonucleotides (col. 3, lines 31-34).

Summerton discloses oligonucleotides having morpholino subunit structures. These oligonucleotides can bind to a target nucleic acid sequence at a temperature above

the normal oligonucleotide melting temperature. This binding at elevated temperatures minimizes the problem of competition for binding to the target between the probe and its single stranded target (col. 16, para. 2).

It would have been obvious to one of ordinary skill in the art, at the time of filing, to modify the teachings of Pollman et al. and Gibbons et al. in view of Agrawal et al. and Summerton et al. in the design of the claimed invention. First it is noted that claim 63 recites an antisense consisting of consecutive nucleotides, the nucleotide sequence of which is set forth in SEQ ID NO: 2. One of ordinary skill in the art seeking alternative antisense compounds effective to inhibit bcl-x expression would have been motivated to design antisense compounds to comprise consecutive nucleotide sequences from the nucleotide sequence of the antisense compound of Pollman et al. according to AS-#3, because the antisense compound comprising the nucleotide sequence of AS-#3 functioned to inhibit bcl-x expression. Additionally, antisense compounds #1 and #2 of Pollman et al. comprised sequences that were truncated forms of AS#3, yet they retained functional activity. Additionally, it would have been obvious to one of ordinary skill in the art to modify the antisense oligonucleotides of Gibbons et al. by modifying those antisense oligonucleotides by the addition of 5-methyl cytidine modified nucleobases (Agrawal), and by the addition of morpholino groups (Summerton) in order to increase hybridization efficiency as well as maintaining nuclease resistance, to provide increased stability of nucleic acid duplexes and to produce fewer side effects than conventional phosphorothioate oligonucleotides (Agrawal).

Therefore, the invention as a whole is *prima facie* over Pollman et al. and Gibbons et al. in view of Agrawal et al. and Summerton et al.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 39-50, and 53-61 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (Written Description).

7. The instant claims are drawn to antisense oligonucleotides or analogs thereof comprising a sequence having 90%, 85%, 80%, 75%, or 70% or greater identity to sequences A, B, C, D, E, F, G, H, I, J, K, L, or M of Figure 1 of the instant application. The specification as filed does not describe the sequence of any antisense oligonucleotide having a sequence that is 90%, 85%, 80%, 75%, or 70% identical to SEQ ID NO: 1-13 of the instant application, wherein said antisense oligonucleotide functions to modulate the expression of human bcl-x expression. The skilled artisan is left to empirically determine whether oligonucleotides having 90%, 85%, 80%, 75%, or 70% identity to SEQ ID NO: 1-13 would function to modulate (increase or decrease) expression of bcl-xl. However, providing a method for isolating and testing the claimed compounds for the recited functionality is not sufficient for providing an adequate description of a compound, especially a biomolecule such as a nucleic acid compound where Applicants do not provide a correlation between the nucleotide sequence of a compound and its functional activity, i.e. increase or decrease expression of bcl-xl. See MPEP § 2163[R-1] which

states that "[T]he claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of theinvention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence."

Additionally, see the January 5, 2001 (Vol. 66, No. 4, pages 1099-1111) Federal Register for the Guidelines for Examination of Patent Applications Under the 35 USC 112 ¶ 1, "Written Description" Requirement. These guidelines state: "[T]o satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention."

In the instant case, apart from further experimentation the skilled artisan would not be able to envision the structures of the full scope of compounds encompassed by the instant claims. Therefore, Applicants were not in possession of the full scope of the claimed compounds at the time of filing of the instant invention.

Double Patenting

8. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

9. Claims 37-62 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 37-62 of copending Application No. 10/160,344. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 9, 26-30, 36, 63, and 65 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 36-54, and 61-62 of copending Application No. 10/160,344. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application are drawn to compositions of matter comprising an antisense oligonucleotide comprising the nucleotide sequence of one of SEQ ID NOS: 1 and 3-13, wherein one or more of the sugar groups of the oligonucleotide contain an –Ome group at its 2' position. Claims are also directed to compositions comprising antisense oligonucleotides comprising the nucleotide sequence of SEQ ID NO: 2 wherein one or more of the sugar groups of the oligonucleotide contain an –Ome group at its 2' position. The claims of the copending application are also drawn to compositions of matter comprising antisense oligonucleotides comprising consecutive nucleotides of SEQ ID NOS: 1-13, nucleotides sequence of which are directed to wherein one or more sugars are modified at its 2' position. The subject matter of the claims of the instant application and that of the claims of the copending application is co-extensive in scope, except in certain cases the claims of the instant application have been amended to claim only SEQ ID NO: 1 and 3-13, or to claim only SEQ ID NO: 2, however the claims of the co-pending application recite SEQ ID NO: 1-13. The claims of the instant application represent an obvious variation of the claims of the co-pending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Notice of Reference Cited

12. It is noted that all references cited in the present Office Action were previously forwarded to Applicants during the prosecution of the instant application.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 571-272-0757. The examiner can normally be reached on Monday-Saturday, Flex Schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Janet L. Epps-Ford, Ph.D.
Examiner
Art Unit 1635

JLE